Paper

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CLINICAL

Dilated cardiomyopathy: a preventable presentation of DiGeorge Syndrome

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ABSTRACT Patients with cardiac failure require careful evaluation to determine the precise nature of the cause of their illness. Genetic causes of dilated cardiomyopathy are well known but inherited conditions may lead to unexpected consequences through intermediate mechanisms not readily recognised as a feature of the inherited disorder. We describe a case of dilated cardiomyopathy resulting from prolonged hypocalcaemia due to previously undiagnosed hypoparathyroidism resulting from DiGeorge Syndrome and describe the features of this case and the treatment of hypoparathyroidism.

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INTRODUCTION

Heart failure is increasingly common and dilated cardiomyopathy (DCM) is a common finding in younger patients who develop systolic heart failure.[1] There are numerous causes of DCM and this report highlights the potential for an inherited condition to be overlooked as a possible unifying diagnosis in patients with chronic conditions. The potential for treatable elements of this condition to result in irreversible long term complications is discussed.

CASE DESCRIPTION

A 45-year-old male attended the emergency department of our hospital because of increasing breathlessness, anorexia and the development of dependent oedema. He had a prior history of epilepsy since the age of 18, for which he received treatment with lamotrigine and sodium valproate, learning difficulties and hypocalcaemia, for which he received a combined calcium and vitamin D supplement (Adcal D3®, 1 tablet twice daily). His adherence to therapy was difficult to ascertain although laboratory records did confirm he had been persistently hypocalcaemic for five years prior to presentation and his serum anticonvulsant levels when measured were within the quoted therapeutic ranges. At the time of seizures he was noted to have sinus tachycardia and no associated arrhythmia. He had previously used cannabis and alcohol in excess, although the excessive alcohol use had been in his early 20s for less than 18 months. Both parents were alive and neither was reported to have had cardiac disease. There was no family history of sudden cardiac death reported.

At the time of admission he was breathless at rest, had a raised jugular venous pressure, a distended abdomen and peripheral oedema. Laboratory tests revealed multiple abnormalities (Table 1). A plain chest radiograph revealed cardiomegaly plus a right-sided pleural effusion, and a 12 lead ECG revealed sinus tachycardia left-axis deviation, poor R wave progression but a normal QRS duration (Figure 1). Computed tomography of the chest, abdomen and pelvis revealed cardiomegaly, intra-aortic thrombus in the descending aorta and bilateral pleural effusions (Figs 2, 3). Further investigations excluded hereditary haemochromatosis, sarcoidosis, copper excess or deficiency, thiamine deficiency and blood borne virus infection. Treatment was commenced with loop diuretics, levothyroxine, magnesium sulphate, alfacalcidol, calcium carbonate and low molecular weight heparin.

Further investigations confirmed primary hypoparathyroidism unresponsive to magnesium replacement and the presence of DCM without evidence of valvular or other congenital heart disease. Left ventricular ejection fraction was estimated at 15% using echocardiography. The patient declined to undergo cardiac MRI due to claustrophobia. Coronary arteries were normal at angiography and left ventriculography showed global hypokinesis. Treatment was modified to include an angiotensin converting enzyme inhibitor, a cardioselective beta blocker and spironolactone, with resolution of oedema, and marked symptomatic improvement. After 8 weeks there was no improvement in left ventricular size or function as assessed by echocardiography. Following treatment of cardiac failure and hypoparathyroidism, laboratory investigations returned to normal suggesting that the initial abnormalities were related to severe cardiac failure

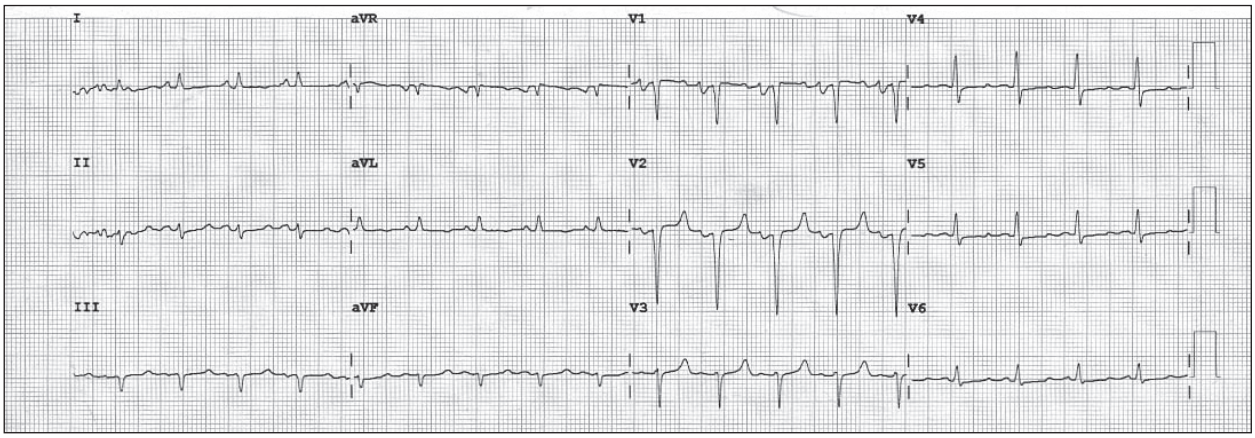

FIGURE 1 Sinus tachycardia. Normal QRS duration, QTc 466ms

TABLE 1 Laboratory parameters at presentation, consistent with primary hypoparathyroidism

	Admission	Day 14
Haemoglobin (g/l) NR (115–160)	124	115
Mean corpuscular volume (fl) NR (78–98)	80	82
White cell count (x 10^9/l) NR (4.0–11.0)	8.2	5.1
Platelets (x 10^9/l) NR (150–400)	99	234
International normalised ratio NR (0.9–1.1)	1.4	1.0
Albumin (g/l) NR (30–45)	24	39
Parathyroid hormone (pmol/l) NR (1.6–6.9)	1.3	
ALT (U/l) NR (10–50)	754	47
AlkPhos (u/l) NR (40–125)	74	112
Phosphate (mmol/l) NR (0.8–1.4)	1.57	0.71
Potassium (mmol/l) NR (3.4–5.0)	2.5	4.9
Calcium (mmol/l) NR (2.1–2.6)	1.04	2.41
Magnesium (mmol/l) NR (0.70–1.00)	0.58	0.78
Folic acid (ug/l) NR (2.8–20)	5.3	
Vitamin B12 (ng/l) NR (180–2000)	375	
Ferritin (ug/l) NR (15–200)	412	193
Serum ACE	Normal	
Serum copper and caeruloplasmin	Normal	
HBV, HCV, HIV	Negative	
HFE gene analysis	Negative	

NR: normal range

and clot load in the arterial system resulting in a mild consumptive coagulopathy (Table 1).

In view of the presence of learning difficulties, epilepsy and hypocalcaemia, genetic testing was performed and confirmed the presence of a deletion of the long arm of chromosome 22, specifically del 22q11.21(18.648,855-21.058,888)x1. This deletion was 2.4Mb in size and was pathogenic in the causation of this illness phenotype, a variant of DiGeorge syndrome.

DISCUSSION

DCM is a common cause of cardiac failure in younger adults.[1] Severe enduring hypocalcaemia related to underlying post-surgical hypoparathyroidsm or coeliac disease is reported to cause DCM and some cases demonstrate reversal of left ventricular dysfunction with restoration of normocalcaemia, although the left ventricular dysfunction may be permanent.[2,3] Our patient had a number of associated abnormalities including arterial and venous thrombosis which are likely sequelae of long standing untreated cardiac failure, a condition that can be associated with multiple thrombotic events.[4]

In this case there was a prolonged period of hypocalcaemia noted from hospital laboratory records (over five years) but there had been no characterisation of the nature or cause of the hypocalcaemia prior to his acute presentation with heart failure. The presence of learning difficulties in association with primary hypoparathyroidism prompted the possibility of DiGeorge syndrome as a cause of the constellation of problems the patient had, even though they had been present in some cases for four decades.

Di George syndrome (OMIM 188400) is a contiguous gene syndrome most commonly due to a deletion of 2.54Mb in a critical portion of the 22q11.2 region of chromosome 22.[5] This region contains the T-box 1 gene, whose gene product is a transcription factor thought to regulate a number of key developmental steps in all mammals.[5] The classical DiGeorge syndrome comprises

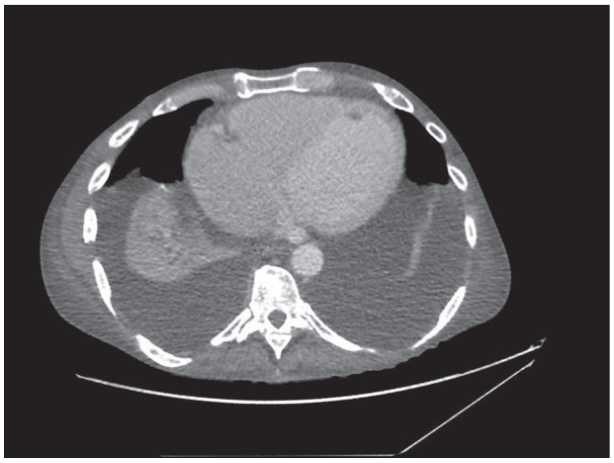

FIGURE 2 CT Thorax demonstrating cardiomegaly and bilateral pleural effusions

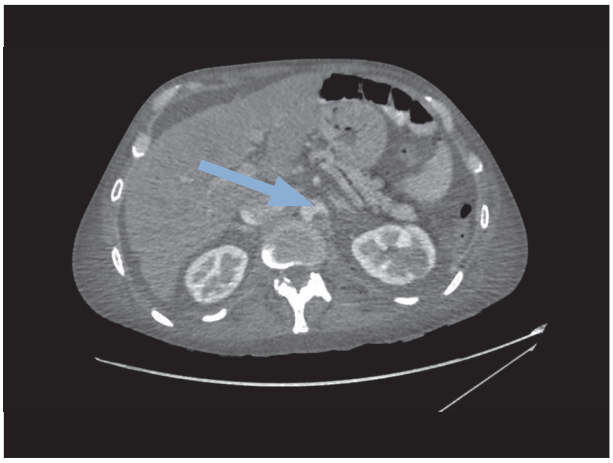

FIGURE 3 CT abdomen demonstrating intra-aortic thrombus (arrow)

hypoparathyroidism (50%), thymic aplasia, congenital heart defects (typically of the cono-truncal type, e.g. Fallot's tetralogy, interrupted aortic arch in 75%) and learning difficulties (60–90%). There are a number of variations of the phenotype where cardiac and other manifestations may be absent, e.g. the velocardiofacial syndrome where palatal and dysmorphic facial features predominate. To our knowledge, the presence of DCM without attendant congenital cardiac lesions has not been reported previously.[5]

Spontaneous hypoparathyroidism is uncommon in adults without a history of neck or thyroid surgery or external beam radiotherapy. In individuals presenting with hypocalcaemia it is essential to take a detailed medical and drug history, e.g. the use of diuretics, proton-pump inhibitors, lack of sunlight exposure, prior neck surgery. If hypocalcaemia is detected, concurrent measurement of serum magnesium, phosphate, parathyroid hormone (PTH) and 25-hydroxy vitamin D are essential for proper determination of the cause of hypocalcaemia. In the presence of hypocalcaemia, a high serum phosphate concentration is typical of hypoparathyroidism. Elevated levels of PTH are likely to point to deficiency of vitamin D, while a very low serum magnesium concentration may cause suppression of PTH secretion and secondary hypoparathyroidism. The presence of a low PTH with a normal serum magnesium concentration and elevated serum phosphate concentration is highly suggestive of primary hypoparathyroidism.

Treatment of hypoparathyroidism requires the concurrent use of oral vitamin D analogues and calcium supplementation. The use of active metabolites of vitamin D, e.g. Calcitriol (1,25 $(OH)_2D_3$) or alfacalcidol ($1\alpha(OH)D_3$) are recommended due to their potency and duration of action while colecalciferol is not recommended. In adults a dose of 1–1.5 mcg of alfacalcidol plus calcium carbonate 500–1000 mg should be used to ensure both serum calcium and phosphate concentrations lie within the normal laboratory ranges.[6]

This case demonstrates the possibility that undiagnosed DiGeorge syndrome may present in the fifth decade with irreversible DCM as a consequence of inadequately treated hypoparathyroidism. This highlights the need for any case of hypoparathyroidism to be adequately investigated to ensure both an accurate diagnosis and optimised treatment to avoid long-term consequences to an individual's health.

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